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Prenatal exposure to organochlorine pesticides and early childhood communication development in British girls

Zuha Jeddy[a], **Katarzyna Kordas**[b], **Kristen Allen**[a], **Ethel V. Taylor**[a], **Kate Northstone**[c], **W. Dana Flanders**[a,d,e], **Gonza Namulanda**[a], **Andreas Sjodin**[a], and **Terryl J. Hartman**[a,d,e,*]

[a]Centers for Disease Control and Prevention, Atlanta, GA, 30341, United States

[b]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, State University of New York, Buffalo, NY, 14214, United States

[c]Bristol Medical School, University of Bristol, Bristol, UK

[d]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, 30322, United States

[e]Winship Cancer Institute, Emory University, Atlanta, GA, 30322, United States

Abstract

Background: The developing brain is susceptible to exposure to neurodevelopmental toxicants such as pesticides.

Aims: We explored associations of prenatal serum concentrations of hexachlorobenzene (HCB), beta-Hexachlorocyclohexane (β-HCH), 2,2-Bis(4-chlorophenyl)-1,1-dichloroethene (p,p'-DDE) and 2,2-Bis(4-chlor-ophenyl-1,1,1-trichloroethane (p,p'-DDT) with maternal-reported measures of verbal and non-verbal communication in young girls.

Study design and methods: We studied a sample of 400 singleton girls and their mothers participating in the Avon Longitudinal Study of Parents and Children (ALSPAC) using multivariable linear regression models adjusting for parity, Home Observation Measurement of the Environment (HOME) score, maternal age and education status, and maternal tobacco use during the first trimester of pregnancy.

Exposure and outcome measures: Maternal serum samples (collected at median 15 wks. gestation [IQR 10, 28]) were assessed for selected organochlorine pesticide levels. Communication was assessed at 15 and 38 months, using adapted versions of the MacArthur Bates Communicative Development Inventories for Infants and Toddlers (MCDI).

*Corresponding author: Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, CNR #3035, Atlanta, GA, 30322, United States. tjhartm@emory.edu (T.J. Hartman).

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neuro.2018.10.003.

Conflicts of interest statement

None declared.

Results: At 15 months, girls born to mothers with prenatal concentrations of HCB in the highest tertile had vocabulary comprehension and production scores approximately 16% (p = 0.007) lower than girls born to mothers with concentrations in the lowest tertile. This association varied by maternal parity in that the evidence was stronger for daughters of nulliparous mothers. At 38 months, girls born to mothers with prenatal concentrations of HCB in the highest tertile had mean adjusted intelligibility scores that were 3% (p = 0.03) lower than those born to mothers with concentrations in the lowest tertile; however, results did not vary significantly by parity. Maternal concentrations of β-HCH and p,p'-DDE were not significantly associated with MCDI scores at 15 or 36 months. p,p'-DDT had an inconsistent pattern of association; a significant positive association was observed between p,p'-DDT with verbal comprehension scores at 15 months; however, at 38 months a significant inverse association was observed for p,p'-DDT with communicative scores. This inverse association for p,p'-DDT among older girls tended to be stronger among daughters of mothers who had lower depression scores. *Conclusions:* Organochlorine pesticide *exposure* in utero may affect communication development.

Keywords

ALSPAC; Language; Communication; Pesticides; In utero exposure; Organochlorines; Prenatal exposure

1. Introduction

Endocrine disrupting chemicals (EDCs) are substances that may change the functioning of the body's endocrine system by binding to and activating various hormone receptors (Akhtar et al., 1996; Cocco, 2002; Leghait et al., 2009; Mnif et al., 2011). Numerous substances identified as pesticides are not only persistent organic pollutants but also act as EDCs and have been shown to disrupt processes involved in sexual maturation and reproduction as well as disturbing neuropsychological development (Saravi and Dehpour, 2016; Andersen, et al., 2002; Kojima et al., 2004; Lemaire et al., 2006; Forns et al., 2012; Vinggaard et al., 2000). These substances are widely diffused in the environment and they accumulate in the fatty tissues of living organisms (Lee et al., 2007; Ribas-Fito et al., 2001; Schafer and Kegley, 2002; Porta, 2004). Humans are exposed to EDCs through inhalation of gases and particles in the air, ingestion of water, food and dust, and absorption through the skin. Pregnant and breastfeeding women who are exposed to EDCs may risk exposing the fetus or child via the placenta or breast milk, respectively (Bergman et al., 2013). Because the endocrine system, which includes adrenal, gonadal, and thyroid hormones, is critical in the neurodevelopment of a fetus (Auyeung et al., 2010; Braun et al., 2014; Henrichs et al., 2013; Ronald et al., 2010), exposure to EDCs in utero can be particularly harmful (Mnif et al., 2011; Birnbaum and Fenton, 2003; Goldman et al., 2004; Sharpe, 2006). Clinical and laboratory studies have documented that a developing brain is especially susceptible to exposures of neurodevelopmental toxicants such as EDCs, even at low levels that may not have noticeable effects on a developed, adult brain (Lee et al., 2007; Schettler, 2001). A recent review highlights research that suggests children exposed to organo-chlorine pesticides early in life may experience adverse effects on memory, attention and communication skills (Saravi and Dehpour, 2016).

Nonverbal and verbal communication are among the first developmental milestones young children achieve. Delayed development of communication and interpersonal behaviors before the age of 3 years may signal developmental disorders or cognitive deficits later in childhood (Braun et al., 2014; American Psychiatric Association, 2010; Centers for Disease Control and Prevention, 2012). Prospective cohort studies have documented that environmental neurotoxicants in maternal or cord blood are adversely associated with cognition in early infancy (Lee et al., 2007; Trask and Kosofsky, 2000). In addition, in the 1999–2000 National Health and Nutrition Examination Survey (NHANES), adverse associations were found between serum concentrations of organochlorine pesticides and self-reported learning disorders in children aged 12–15 years (Lee et al., 2007; Jacobson and Jacobson, 2005). More information is needed to determine how exposures to organochlorines can affect communication and cognition in young children as well as the development of disorders later in life.

In population-based studies, infant/child communication and development are often measured through parent-reported assessments. The MacArthur Bates Communicative Inventory (MCDI) (Feldman et al., 2000; Fenson et al., 1993; SanGiovanni et al., 2000) has been widely used to measure verbal and non-verbal communication in young children (Ellawadi and Ellis Weismer, 2014). Items associated with abnormal communication and interpersonal behaviors include delayed onset of talking, late understanding of spoken language and intent to communicate or show gestures, relative to expectations for age (Rice et al., 2013).

Our objective was to evaluate the association between intrauterine exposure to selected organochlorine pesticides and the development of communication skills in young girls. The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort of mother-child pairs. The study contains information relating to pregnancy and birth characteristics, demographic factors, and childhood behavioral outcomes. Access to maternal prenatal serum samples that were previously analyzed for organochorine pesticides offered an ideal opportunity to explore associations between in utero exposure to these EDCs and childhood communication development outcomes measured in girls at 15 and 38 months of age.

2. Methods

2.1. Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective cohort study designed to investigate the development and health of children in the South West of England (Fraser et al., 2013). Recruitment methods have been described in detail (Boyd et al., 2013; Maisonet et al., 2012). Pregnant women expected to deliver between April 1991 and December 1992 in three health districts in the former county of Avon were enrolled and followed prospectively (n = 14,541). The cohort included 14,062 live births. Serum samples were taken at mothers' enrollment and were processed and frozen for analysis later; the median gestational age of sample collection was 15 weeks (interquartile range - (IQR = 10.0, 28.0). Questionnaires were mailed four times during pregnancy, and at set time points postnatally, to collect information on demographics, health status, lifestyle characteristics, and behavioral and cognitive outcomes of the child. The study website contains additional

details for all available data through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee, the Local Research Ethics Committees, and the Centers for Disease Control and Prevention (CDC) Institutional Review Board. Mothers provided written informed consent for participation in the study.

The participants in the current study were drawn from an ancillary study of puberty and development including singleton, active, female participants at the age of 13 years in 2004–2005 and their mothers. Two valid assessments of pubertal status between the ages of 8 and 13 were returned by 3682 girls. From this group, a nested case-control study of 448 mother-daughter dyads was designed to explore the effects of environmental exposures (measured in maternal serum and urine) on selected health outcomes. The ancillary study included all girls with early menarche (< 11.5 years) and a random sample of girls without early menarche (≥ 11.5 years) (Maisonet et al., 2012). The present study includes 400 girls who had values for childhood communication assessments at 15 or 38 months and maternal serum concentrations of organochlorine pesticides and lipids (n = 194 with early meanarche and 206 without early menarche).

2.2. Cognitive measures

At 15 months and 38 months of age, mothers were mailed ALSPAC-adapted versions of the MacArthur Communicative Development Inventory (MCDI), which evaluates vocabulary comprehension and social activity in children (Feldman et al., 2000; Fenson et al., 1993; SanGiovanni et al., 2000) based on behaviors at the time of evaluation. The ALSPAC adaptation of the MCDI at 15 months includes verbal comprehension, verbal production, nonverbal communication and social development scores. The verbal comprehension score (range 0–12) was compiled from 12 questions, which ask if the child understands phrases such as “time for bed” and “come here.” The vocabulary comprehension and production score (range 0–268) was compiled from 133 questions in which parents indicated whether the child understands but doesn’t speak or understands and speaks words such as “dog” and “milk.” Nine questions asking if the child completes actions such as “blows kisses from a distance” or “shakes head ‘no’” were used to derive the nonverbal communication score (range 0–20). To derive the social development score (range 0–32), 15 questions asking if the child completes actions such as “puts on a shoe or sock” or “brush teeth” were compiled. The 38-month questionnaire included three sub-scores (range): language (8–326), intelligibility (0–6), and communicative (Mnif et al., 2011; Saravi and Dehpour, 2016; Andersen et al., 2002; Kojima et al., 2004; Lemaire et al., 2006; Forns et al., 2012; Vinggaard et al., 2000; Lee et al., 2007; Ribas-Fito et al., 2001). The language sub-score at 38 months evaluates vocabulary, use of plurals, past tense, and word combinations. Each increment of the score corresponds to a degree of communication development within each domain. At both ages, higher sub-scores indicate greater communication development.

2.3. Laboratory measures

Laboratory analysis was done at the National Center for Environmental Health of the Centers for Disease Control and Prevention (CDC) (Atlanta, GA). The samples were measured for serum concentrations of hexachlorobenzene (HCB), β-Hexachlorocyclohexane

(β-HCH), 2,2-Bis(4-chlorophenyl)-1,1-dichloroethene (p,p'-DDE) and 2,2-Bis(4-chlorophenyl-1,1,1-trichloroethan (p,p'-DDT) using established methods (36 Briefly, the serum samples were fortified with ^{13}C-labeled internal standards and diluted with formic acid and water followed by solid phase extraction (SPE). Co-extracted lipids were performed on a silica/silica-sulfuric acid column and final determination of target analytes were made using gas chromatography isotope dilution high resolution mass spectrometry (GC/ID-HRMS). Limit of detection (LOD) and recovery of ^{13}C-labeled internal standards are given in Supplemental Table 1. Each sample batch included 24 unknown, 3 method blanks, and 3 quality control (QC) samples. The LOD was defined as the highest LOD calculated using two methods: (*i*) lowest point in the calibration curve having a signal-to-noise ratio greater than 10:1 and (*ii*) three times the standard deviation of detected interferences in the method blanks samples measured in parallel with the unknown samples. The following quality control criteria had the met for a measurement in a batch of samples to be considered valid and reportable: (*i*) the measurement of the target analyte in the QA/QC sample must not fall outside the interval defined as plus/minus three standard deviations of the established mean of the QA/QC samples and (*ii*) 10 or more consecutive measurements of the QA/QC sample may not fall above or below the established mean of the QA/QC samples after one QA/QC sample has failed criterion (i). Further, every measurement of a set of samples must fulfill the following criteria to be considered a valid measurement: (*i*) The ratio of the two ions monitored for every analyte and ^{13}C-labeled internal standard must not deviate more then 20% from the theoretical value. (*ii*) The ratio of the retention time of the analyte over its corresponding ^{13}C-labeled internal standard must be within the range 0.99–1.01. (iii) The measured recovery of the IS must be within the range 25–150% (Sjodin et al., 2004).

Maternal serum concentrations served as a proxy for fetal exposure. HCB is created as a by-product from the manufacturing of other chemicals (US Environmental Protection Agency, 2018a). The production of lindane, an insecticide, creates HCB as a byproduct (Porta et al., 2013). p,p'-DDE is a result of the breakdown of p,p'-DDT in the environment (US Environmental Protection Agency, 2018b). Analytical methods have been described elsewhere (SanGiovanni et al., 2000; Fraser et al., 2013). Pesticide concentrations were reported as lipid-adjusted (ng/g lipid) after correction for total serum lipid levels. Limits of detection (LOD) were proportional to the available serum amount (5th and 95th percentile: 0.35–1.1 g) and lipid concentration (5th and 95th percentile: 410–937 mg/dL). LOD were determined individually for each reported pesticide defined as the highest of three times the standard deviation of blanks analyzed in parallel with the unknowns and the lowest calibration point having a signal to noise ratio greater than three (Sjodin et al., 2014). Estimated values for pesticide measurements below the limit of detection (LOD - ranging from 1.52% of samples for P-HCH and 11.25% of samples for p,p'-DDT) were calculated by dividing the LOD by the square root of 2 (Croghan and Egeghy, 2003).

2.4. Covariates

Potential confounders based on previous literature and biological plausibility included: parity (nulliparous, ≥1); maternal education (< O level, O level, > O level), where O-level is the qualification obtained at age 16 when required schooling ends; maternal smoking during the first trimester of pregnancy (yes, no); alcohol use during the first trimester of pregnancy

(yes, no); low birthweight defined as less than 2500 g (yes, no); gestational age at birth (weeks); maternal antepartum depressive symptoms measured using the Edinburgh Postnatal Depression Scale (EPDS; range 0–30) (Friesen et al., 2017; Gibson et al., 2009), which in the current study was used to assess depression beginning in or extending into pregnancy; breastfeeding duration (weeks) (Crisp et al., 1978); gestational age when the serum sample was collected (weeks), and an adapted version of the Home Observation for Measurement of the Environment (HOME) score at 6 and 18 months (range 0–12) which measures the developmental stimulation of the home environment (Bradley, 1993). Final inclusion in the models for each potential confounder required meeting the following criteria: biological plausibility, statistical significance in relation to communication outcome of interest, and inclusion/exclusion of the variable from the model changed the parameter estimates for the exposure variable by ≥ 10.

2.5. Statistical analysis

The sample of girls obtained for analysis was previously selected to use in a nested case-control study examining associations of EDCs and age at menarche. To account for the sampling selection probabilities, we conservatively constructed stratum-weighted linear regression models to account for the sampling scheme used for participant selection, assigning the weighting of 15.1 to the girls who attained menarche at an older age (a random sample of the larger population of all the ALSPAC girls who attained menarche ≥ 11.5 years of age) and a weight of 1 to girls who attained menarche at < 11.5 years 1 (Richardson et al., 2007). Serum concentrations of four organochlorine pesticides were analyzed as categorical (tertile) variables (Tables 2–5). The categorized variables do not assume linearity and influence of outlying data points is constrained. However, results for continuous exposure variables are available in Supplemental Tables 3–6.

The pesticides and MCDI subset scores were examined for potential outliers. The relationships between potential covariates and the pesticides were then explored in univariate analyses. Multivariable linear regression models were constructed separately for outcomes at 15 and 38 months due to item and scoring differences. Final parsimonious models were achieved through assessment of variables in a hierarchical manner (Kleinbaum et al., 1982). The final model for 15-month out-comes included parity, maternal age, maternal smoking during early pregnancy, and HOME score at 6 months. The final 38-month models included parity, maternal age, maternal education status, and HOME score at 18 months. For presentation, we calculated adjusted means and 95% confidence intervals (95% CI) of MCDI scores by tertiles of maternal pesticide exposures after adjusting for covariates. Tests of trend were conducted in final multivariable models by assigning the median value from each tertile of pesticides and modeling this value as a continuous variable. Parity and maternal depression score were selected *a priori* to be evaluated for effect modification by testing appropriate cross-product interaction terms with continuous pesticide variables in final models and by stratified analysis (parous/nulliparous, EPDS split at the median ≤6/ > 6). P-values of < 0.05 were used to determine significance. SAS version 9.3 (SAS Institute Inc., Cary, NC) was used to conduct all analyses.

3. Results

Table 1 and Supplemental Table 1 present sample characteristics for mother-daughter dyads. Median pesticide concentrations were higher among older mothers; Spearman correlation coefficients for continuous age with organochlorine pesticides were as high as 0.52 for β-HCH. Median pesticide levels also tended to be higher among girls who had lower birthweight; however, there were few (≤ 5%) in this category. Spearman correlation coefficients between MCDI sub-group scores ranged 0.39–0.64 at 15 months and 0.20–0.28 at 38 months. Spearman correlation coefficients between communication subscales (which are not the same at the two time points) measured at the two ages ranged, 0.03–0.35 (data not presented). Overall, the median values of lipid-adjusted HCB and P-HCH were similar, at 50.2 ng/g lipid (interquartile range (IQR) 37.8, 63.5) and 47.2 ng/g lipid (IQR 34.6, 62.5), respectively (Table 1). There was a strong correlation between these two analytes, with a Spearman correlation coefficient of 0.82. The median value of p,p'-DDE, 309.5 (IQR 192.5, 496.0) ng/g lipid, was many times that of p,p'-DDT, 11.4 ng/g lipid (IQR 34.6, 62.5) (Table 1). The Spearman correlation coefficient between these two analytes was 0.74.

3.1. Prenatal exposures and communication scores at 15 months

There were no associations for maternal concentrations of β-HCH or p,p'-DDEwith daughters' MCDI scores at 15 months although there was some evidence of an inverse association between p,p'-DDE and non-verbal communication (Table 2). An unexpected finding was a positive association between p,p'-DDT with verbal comprehension scores at 15 months. At 15 months, there was an inverse association between HCB and vocabulary comprehension and production; no associations were observed for nonverbal communication, social development, and verbal comprehension scores. In adjusted models, girls born to mothers with prenatal concentrations of HCB in the highest tertile (T_3) had vocabulary comprehension and production scores approximately 16% lower than those born to mothers with concentrations in the lowest tertile (T_1). At 15 months, the association for maternal HCB with two of the three MCDI subscale scores varied by maternal parity. In stratified analyses (Table 3), although patterns of association for both parous and nulliparous women were similar, associations between daughters' MCDI scores (verbal comprehension and vocabulary comprehension and production) with mother's concentrations of HCB were inverse only for nulliparous mothers.

3.2. Prenatal exposures and communication scores at 38 months

There were no strong associations between either β-HCH or p,p'- DDE and communication development scores at 38 months. At 38 months (Table 4), girls born to mothers with prenatal concentrations of HCB in the highest tertile had mean adjusted intelligibility scores that were approximately 3% lower than those born to mothers with concentrations in the lowest tertile; however, unlike at 15 months, the 38-month associations did not vary by maternal parity. In contrast to the results for younger girls, at 38 months, p,p'-DDT was inversely associated with communicative scores. In adjusted models, at 38 months, girls exposed to the highest prenatal p,p'-DDT levels had communicative scores approximately 7.7% lower than those in the lowest exposure group. Two analytes, p,p'-DDE and HCB showed some evidence for inverse associations with the language subscale score. In

stratified analyses, the inverse association for p,p'-DDT and daughters' communicative scores (observed in main effects models) was significant only when maternal depression scores were lower (e.g., less likely to be depressed - Table 5). There were no consistent patterns of association between p,p'-DDT and the other MCDI subscale scores within strata of maternal depression scores.

4. Discussion

Although many pesticides, including HCB, β-HCH, p,p'-DDE, and p,p'-DDT, were once widely used, they are now prohibited in most parts of the world (Sjodin et al., 2004; Porta et al., 2013; US Environmental Protection Agency, 2018c; Rogan and Chen, 2005). Nevertheless, they still persist in the environment, and bioaccumulate in invertebrate and vertebrate tissues (Mnif et al., 2011). In the serum of pregnant British women, of the pesticides we evaluated, p,p'-DDE concentrations were the highest (median 309.5 ng/g lipid). In comparison, a pooled analysis of European birth cohorts with maternal prenatal samples collected between 2000 and 2006 (Iszatt et al., 2015) reported median prenatal concentrations of p,p'-DDE ranging between 42.1 (Norway) and 413.5 (Slovakia) ng/g lipid. p,p'-DDE is formed as p,p'-DDT breaks down in the environment and is more persistent than p,p'-DDT in most populations (Rogan and Chen, 2005). Humans are most commonly exposed to p,p'-DDE through foods, particularly meats, poultry, and fish (Sjodin et al., 2004).

Current literature presents mixed evidence regarding the effects of pesticide exposure in utero on cognition and communication in early childhood. This may be in part because the effects of environmental contaminants like organochlorine pesticides are most often subtle with only modest effects observed at the individual level. In addition, investigators have used different study design, methods and instruments to evaluate these outcomes among young children at different ages. Several studies have explored the effects of pesticide exposure on developmental scores of children using tools such as the Bayley Scales of Infant Development (BSID) (Jurewicz et al., 2013); however, we are not aware of any studies evaluating the effects of pesticide exposure in utero on the development and communication abilities in children at 15 or 38 months using the MCDI. Current literature suggests that intrauterine exposure to p,p'-DDT and p,p'-DDE may impair psychomotor development in the first year of life (Eskenazi et al., 2007; Ribas-Fito et al., 2003; Torres-Sanchez et al., 2007). For example, in a Mexican study, trained psychologists blinded to maternal p,p'-DDE exposure level, administered the BSID to 244 children during the first year of life. p,p'-DDE serum levels during the first trimester of pregnancy were associated with a decrease in the psychomotor development index (PDI) but not the mental development index (MDI) (Jurewicz et al., 2013; Torres-Sanchez et al., 2007). Similarly, a study of 360 children tested at ages 6, 12 and 24 months in California showed that for each 10-fold increase in p,p'-DDT levels at 6 and 12 months and p,p'-DDE levels at 6 months, infants scored 2-points lower on the PDI (Jurewicz et al., 2013; Eskenazi et al., 2007). Cord blood p,p'-DDE levels were inversely associated with both MDI and PDI, but HCB was not associated with neurodevelopment in one year old Spanish infants (Kleinbaum et al., 1982). A New York study of 263 women and their infants assessed cognition using the Fagan Test for Infant Intelligence (FTII) administered at 6 and 12 months and found no strong associations

between FTII scores and cord blood p,p'-DDE levels (Jurewicz et al., 2013; Darvill et al., 2000). Kostyniak et al. (1999) evaluated the association between prenatal exposure to p,p'-DDE and behavioral development among 11,018 5–9 year old children from Greenland and the Ukraine, The investigators used a 25-item questionnaire which assessed strengths and difficulties overall and for five sub-scales including emotional and conduct issues, hyperactivity, peer relationships and social behavior. A doubling of exposure was positively associated with difficulties with conduct (OR = 1.25, 95% CI 1.04, 1.51) and hyperactivity (OR = 1.43, 95% CI 1.06, 1.92) but failed to reach statistical significance for overall total difficulties (OR 1.15, 95% CI 0.90, 1.48) (Kostyniak et al., 1999).

Similar to previous investigations, our results did not show a consistent pattern of association across all organochlorines measured at both the time points. For example, at 15 months of age, we observed inverse associations between maternal HCB and vocabulary comprehension and production. At 38 months of age, we observed less apparent inverse associations between HCB and MCDI components (e.g., intelligibility and language scores), although direct comparisons are not possible given the item and format differences between the questionnaires. In addition, the associations between maternal organo-chlorine concentrations and early communication development tended to vary by parity status, while later communication development tended to vary by maternal depression. Parity may be a proxy for a number of potential influences on childhood communication development including interactions with other siblings or at childcare. Because these pesticides may accumulate in fat tissue, parity may also reflect opportunity for reduced bioaccumulation because of previous pregnancies and breast feeding (Zong et al., 2016). For example, among a large cross-sectional sample of parous women in the NHANES, self-reported breast feeding history was inversely associated with current levels of persistent organic pollutants (Pawlby et al., 2011). Both parity and maternal depression may also be related to the quality and quantity of the mother's time, interest, and attention given to the development of cognitive and communication skills (Eriksen et al., 2013; Lawlor et al., 2005; Hibbeln et al., 2007).

Possible sources of exposure to pesticides could have been through the consumption of animal products, particularly meats and dairy, that contain animal fat in which the pesticides may have bio accumulated. Exposure from contaminated water, dust or soil is also possible, but less likely (Soltaninejad and Abdollahi, 2009). When pesticides are present in the body, they may act as endocrine disruptors. This is especially harmful to a developing fetus, and could be one mechanism by which pesticide exposure in utero affects the communication and development of a child (Lee et al., 2007). Biological mechanisms such as oxidative stress or DNA damage could also have long-term effects on neurodevelopment (Eriksson et al., 1992). In animal models, neonatal exposure to EDCs, including p,p'-DDT and p,p'-DDE, has been associated with permanent effects on the cerebral cortex and on behavior (Johansson et al., 1996).

There are multiple strengths to this study. The sample was a large, prospective, well-characterized population of pregnant women and their infants. The organochlorine pesticides were measured using well-characterized procedures at the laboratories of the National Center of Environmental Health at the CDC. In addition, we used the MCDI scale, which is

well-known and frequently employed to measure childhood communication development, and we were able to examine communication abilities at two time points during early childhood, thus contributing to the understanding of potential persistence of effects.

However, there are also several limitations to this study. We analyzed data from a population originally selected for an ancillary study with a different focus, which may introduce bias. However, as reported previously, maternal characteristics for girls included in the ancillary sample were similar to the group of girls enrolled in the overall cohort (Maisonet et al., 2012) and linear regression models were weighted to account for the sampling scheme (Richardson et al., 2007). Our sample with data for both maternal organochlorine and daughters' MCDI scores was also relatively representative of the overall ancillary sample. For example, in the overall ancillary sample and in our sample-20% of mothers were in the lowest educational group; in the overall ancillary sample-23% of mothers reported prenatal smoking compared to 21.5% in the current study. Lastly, in both samples 42% of mothers were 30 years of age or older at delivery. Blood samples obtained at multiple time points during pregnancy may provide a more accurate estimate of intrauterine exposure; our study only measured serum levels at one time point. Additionally, in our study a small number of pesticides had values below the limit of detection. To correct for this, the LOD was divided by the square root of two to give a value to those below the LOD. Although an accepted procedure, it is possible that this estimation is not representative of the actual exposure. In this analyses where exposures were analyzed by tertiles this is not likely to affect our overall results. The MCDI scores were self-reported by the mothers which can be problematic if mothers over-estimate their children's performance. Unfortunately, we cannot make direct comparisons between the two time points where communication was assessed because there are differences in the items and format of the questionnaires at 15 and 38 months. In addition, maternal lead and mercury levels, which may also affect early childhood cognition and communication were not assessed as potential covariates as they were unavailable for more than half of the population. Lastly, although these data showed that 15 month old girls born to mothers with prenatal concentrations of HCB in the highest tertile had vocabulary comprehension and production scores approximately 16% lower than girls born to mothers with concentrations in the lowest tertile it is unknown whether this difference may be associated with persistent language difficulties.

5. Conclusion

Results from this study suggest that organochlorine pesticide exposure in utero may negatively affect communication development. Further research is needed to determine specifically how pesticides affect neurodevelopment in early life and which pesticides may have the most deleterious effects and at which time points during development. In addition, the current study does not include results for boys as organochlorine pesticide levels were not measured among mothers of boys. Conducting similar research in cohorts that include boys would provide additional information about the association between prenatal organochlorine pesticide exposure and early childhood communication development in boys.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of study population by level of lipid-adjusted pesticides (ng/g lipid).

	Frequency n (%)	p,p'-DDE Median (IQR)*	p,p'-DDT Median (IQR)*	HCB Median (IQR)*	β-HCH Median (IQR)*
Overall	400	309.5	11.4	50.2	47.2
		(192.5, 496.0)	(8.1, 16.5)	(37.8, 63.5)	(34.6, 62.5)
Maternal age at delivery (yrs)					
< 25	78	178.0	9.0	36.4	33.7
	(19.5)	(135.0, 288.0)	(7.3, 11.6)	(31.0, 46.2)	(26.8, 40.7)
25–29	154	286.5	10.6	47.9	45.0
	(38.5)	(193.0, 422.0)	(8.3, 14.8)	(38.3, 59.0)	(35.4, 56.5)
≥30	168	451.0	14.7	59.9	57.3
	(42)	(283.0, 623.0)	(9.4, 19.9)	(45.1, 70.3)	(45.3, 74.5)
Maternal education					
Low	77	288.0	11.3	46.7	42.4
	(19.3)	(184.0, 446.0)	(7.6, 15.7)	(33.1, 62.7)	(32.7, 60.5)
Medium	128	257.0	9.9	45.1	41.6
	(32)	(164.0, 455.50	(7.7, 14.6)	(36.1, 58.8)	(32.6, 54.6)
High	183	389.0	12.7	54.2	53.1
	(45.8)	(229.0, 541.0)	(8.6, 18.4)	(42.6, 67.3)	(40.9, 67.2)
Missing	12	276.5	9.9	45.9	47.7
	(3.0)	(176.0, 506.5)	(8.4, 17.7)	(33.7, 61.9)	(37.0, 76.5)
	Frequency n (%)	**p,p'-DDE(pg/g) Median (IQR)**	**p,p'-DDT (pg/g) Median (IQR)**	**HCB (pg/g) Median (IQR)**	**β-HCH (pg/g) Median (IQR)**
Maternal prepregnancy BMI (kg/m)					
< 18.5	15	326.0	11.2	40.8	47.9
	(3.8)	(176.0, 522.0)	(8.4, 13.2)	(30.8, 52.7)	(34.9, 63.5)
18.5–24.9	263	331.0	10.6	50.8	47.5
	(65.8)	(198.0, 516.0)	(7.7, 16.2)	(37.8, 63.9)	(35.3, 64.8)
25–29.9	58	315.5	12.2	46.1	45.0
	(14.5)	(206.0, 478.0)	(9.6, 18.0)	(38.3, 65.1)	(34.1, 56.8)

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	Frequency n (%)	p,p'-DDE Median (IQR)*	p,p'-DDT Median (IQR)*	HCB Median (IQR)*	β-HCH Median (IQR)*
> 30	27	306.0	15.0	55.3	51.7
	(6.8)	(217.0, 599.0)	(11.2, 28.5)	(43.6, 68.0)	(33.6, 67.9)
Missing	37	243.0	11.1	47.2	41.1
	(9.3)	(160.0, 350.0)	(7.7, 14.1)	(33.4, 58.9)	(32.0, 55.0)
Maternal Alcohol Use					
Yes	181	331.0	12.7	53.7	50.3
	(45.3)	(213.0, 524.00	(9.0, 17.3)	(39.6, 67.4)	(35.6, 67.2)
No	205	295.0	10.2	46.3	45.3
	(51.3)	(175.0, 482.0)	(7.7, 14.9)	(36.4, 59.8)	(33.6, 56.1)
Missing	14	241.5	9.9	43.2	40.7
	(3.5)	(160.0, 350.0)	(6.4, 22.9)	(31.8, 59.7)	(32.0, 66.2)
Maternal Smoking Status					
Yes	86	290.0	10.9	44.0	45.3
	(21.5)	(168.0, 412.0)	(8.0, 14.2)	(35.5, 62.1)	(34.6, 60.5)
No	301	331.0	11.6	50.9	47.5
	(75.3)	(205.0, 516.0)	(8.4, 17.0)	(39.4, 64.2)	(35.0, 63.1)
Missing	13	234.0	9.8	44.4	40.3
	(3.3)	(160.0, 339.0)	(6.4, 18.9)	(33.4, 59.7)	(32.0, 62.4)
	Frequency n (%)	**DDE(pg/g) Median (IQR)**	**DDT (pg/g) Median (IQR)**	**HCH (pg/g) Median (IQR)**	**HCH (pg/g) Median (IQR)**
Previous Live Birth					
Yes	191	323.0	11.0	51.2	48.2
	(47.6)	(193.0, 509.0)	(7.8, 16.1)	(38.4, 62.2)	(34.9, 63.8)
No	193	308.0	11.6	50.2	46.9
	(48.3)	(198.0, 493.0)	(8.6, 17.7)	(37.9, 65.3)	(34.7, 60.3)
Missing	16	216.5	9.8	43.2	39.6
	(4.0)	(158.5, 314.0)	(5.9, 18.9)	(32.6, 60.4)	(30.2, 58.2)
Low Birth Weight (< 2,500 g)					
Yes	20	528.5	17.9	56.2	61.8
	(5.0)	(321.0, 994.0)	(8.0, 22.2)	(46.2, 75.5)	(52.7, 83.1)

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	Frequency n (%)	p,p'-DDE Median (IQR)*	p,p'-DDT Median (IQR)*	HCB Median (IQR)*	β-HCH Median (IQR)*
No	380	302.5	11.1	49.9	46.0
	(95.0)	(186.5, 484.0)	(8.1, 16.1)	(37.2, 62.8)	(34.4, 60.4)
Preterm Delivery (<37 wks gestation)					
Yes	12	274.0	10.4	54.4	54.6
	(3.0)	(224.5, 638.5)	(10.0, 18.6)	(47.8, 69.5)	(43.0, 76.1)
No	388	311.0	11.4	49.9	46.9
	(97.0)	(189.0, 492.0)	(8.1, 16.5)	(37.5, 63.4)	(34.5, 61.5)
	Frequency n (%)	**DDE(pg/g) Median (IQR)**	**DDT (pg/g) Median (IQR)**	**HCH (pg/g) Median (IQR)**	**HCH (pg/g) Median (IQR)**
Breastfeeding Duration					
Never	79	293.0	10.8	46.3	42.4
	(19.8)	(164.0, 472.0)	(8.0, 15.1)	(35.2, 59.6)	(34.1, 56.1)
< 3 months	98	293.5	11.5	51.8	45.8
	(24.5)	(203.0, 516.0)	(8.2, 15.0)	(40.2, 65.3)	(34.4, 59.5)
3–5 months	61	337.0	12.7	50.8	48.9
	(15.3)	(219.0, 482.0)	(9.0, 20.4)	(40.2, 65.3)	(38.5, 63.8)
≥ 6 months	158	318.5	11.2	49.8	50.0
	(39.5)	(198.0, 522.0)	(7.9, 17.3)	(36.6, 65.7)	(34.6, 67.0)
Missing	4	391.5	14.9	50.2	51.9
	(1.0)	(214.2, 458.0)	(10.5, 19.6)	(46.8, 75.8)	(46.7, 67.3)

*IQR = interquartile range.

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Table 2

Association between maternal organochlorine pesticide exposure and communication development scores in daughters at 15 months.*

	Nonverbal Communication		Social Development		Verbal Comprehension		Vocabulary Comprehension & Production	
Analyte Tertiles (ng/g lipid)	**Adjusted mean (95% CI)**	**P*****	**Adjusted mean (95% CI)**	**P*****	**Adjusted mean (95% CI)**	**P*****	**Adjusted mean (95% CI)**	**P*****
p,p'-DDE (n = 375)								
1 (≤ 229.5)	15.38 (14.76, 15.07)		18.77 (17.67, 19.86)		9.77 (9.32, 10.21)		97.27 (88.71, 105.84)	
2 (229.51–420.0)	14.52 (13.96, 15.08)	0.94	18.35 (17.36, 19.35)	0.97	9.42 (0.01, 9.83)	0.46	95.05 (87.30, 102.81)	0.76
3 (> 420.0)	14.48 (13.90, 15.07)	0.06	18.33 (17.29, 19.36)	0.59	9.64 (9.22, 10.06)	0.71	96.80 (88.72, 105.84)	0.94
p-trend**	0.11		0.65		0.93		0.98	
p,p'-DDT (n = 363)								
1 (≤ 9.0)	14.88 (14.31, 15.44)		17.80 (16.79, 18.81)		9.29 (8.88, 9.70)		94.98 (86.99, 102.97)	
2(9.01–14.7)	14.57 (14.01, 15.14)	0.17	19.02 (18.01, 20.02)	0.73	9.45 (9.04, 9.87)	0.04	99.21 (91.24, 107.18)	0.66
3 (> 14.7)	15.16 (14.55, 15.77)	0.52	18.76 (17.67, 19.85)	0.22	10.10 (9.65,	0.01	96.57 (87.94, 101.21)	0.80
p-trend**	0.40		0.31		10.54) 0.008		0.88	
HCB (n = 375)								
1 (≤ 41.2)	14.92 (14.31, 15.52)		18.35 (17.29, 19.41)		9.70 (9.26, 10.13)		105.38 (97.12, 113.64)	
2 (41.21–59.0)	15.20 (14.66, 15.75)	0.02	19.26 (18.29, 20.22)	0.04	9.85 (9.45,	0.05	95.60 (88.11, 103.08)	0.21
3 (> 59.0)	14.19 (13.57, 14.80)	0.12	17.77 (16.69, 18.84)	0.47	10.24) 9.25 (8.81,	0.19	88.35 (80.00, 96.71)	0.01
p-trend**	0.10		0.43		9.70) 0.17		0.007	
β-HCH (n = 374)								
1(< 39.05)	15.26 (14.61, 15.92)		19.56 (18.40, 20.71)		9.94 (9.47, 10.41)		104.54 (95.55, 113.53)	
2 (39.06–56.15)	14.58 (14.04, 15.11)	0.95	17.81 (16.88, 18.75)	0.49	9.61 (9.22, 9.99)	0.39	93.51 (86.23, 100.79)	0.91
3 (≥ 56.15)	14.61(14.01, 15.20)	0.18	18.32 (17.27, 19.36)	0.14	9.35 (8.92, 9.78)	0.09	92.83 (84.67, 101.00)	0.08
p-trend**	0.25		0.28		0.10		0.12	

*Adjusted for home score at six months, maternal age, parity, smoking status. Pesticides lipid-adjusted with units ng/g lipid.

**P-trend based on a scored variable using the median value of each tertile.

***P-values based on the comparison between the category with the lowest category (referent).

Table 3

Association between maternal organochlorine pesticide exposure and communication development scores in daughters at 15 months by strata of parity.*

Analyte Tertiles (ng/g lipid)	Nonverbal Communication Adjusted mean (95% CI)	P***	Social Development Adjusted mean (95% CI)	P***	Verbal Comprehension Adjusted mean (95% CI)	P***	Vocabulary Comprehension & Production Adjusted mean (95% CI)	P***
Nulliparous women								
HCB (n = 189)								
1 (≤ 41.2)	14.56 (13.75, 15.37)		18.05 (16.53, 19.57)	0.07	9.96 (9.37, 10.55)		113.39 (101.28,125.49)	
2 (41.21–59)	15.32 (14.67, 15.98)	0.16	19.29 (17.95, 20.63)	0.07	10.10 (9.58, 10.62)	0.01	103.02 (92.34, 113.70)	0.11
3 (> 59.0)	14.02 (13.32, 14.73)	0.89	17.32 (15.67, 18.97)	0.56	8.97 (8.33, 9.61)	0.04	88.99 (75.85, 102.12)	0.01
p-trend**	0.90		0.56		0.04		0.01	
Parous women								
HCB (n=187)								
1 (≤ 41.2)	15.07 (14.13, 16.01)		18.63 (17.13, 20.13)		9.51 (8.87, 10.16)		97.43 (85.90, 108.96)	
2 (41.21–59)	15.05 (14.17, 15.93)	0.26	19.44 (18.04, 20.85)	0.43	9.65 (9.05, 10.25)	0.73	87.01 (76.21, 97.80)	0.91
3 (> 59.0)	14.30 (13.36, 15.24)	0.28	18.61 (17.13, 20.13)	0.99	9.50 (8.86, 10.13)	0.98	87.93 (85.90, 108.96)	0.27
p-trend**	0.26		0.95		0.96		0.28	

*Adjusted for home score at six months, smoking status, and maternal age. Pesticides lipid-adjusted with units ng/g lipid.

**P-trend based on a scored variable using the median value of each tertile.

***P-values based on the comparison between the category with the lowest category (referent).

Table 4

Association between maternal organochlorine pesticide exposure and communication development scores in daughters at 38 months.*

Analyte Tertiles (ng/g lipid)	Communicative Adjusted mean (95% CI)	P***	Intelligibility Adjusted mean (95% CI)	P***	Language Adjusted mean (95% CI)	P***
p,p'-DDE (n = 339)						
1 (≤ 234)	5.06 (4.86, 5.26)		5.82 (5.71, 5.93)		310.60 (305.73, 315.47)	
2 (234.1–445)	5.12 (4.95, 5.30)	0.08	5.90 (5.81, 5.99)	0.33	302.80 (298.51, 307.08)	0.96
3 (≥ 445)	4.90 (4.73, 5.08)	0.27	5.83 (5.73, 5.93)	0.90	302.62 (298.12, 307.12)	0.03
p-trend **	0.17		0.89		0.05	
p,p'-DDT (n = 331)						
1 (≤ 9.2)	5.22 (5.03, 5.41)		5.78 (5.68, 5.88)		302.98 (298.39, 307.57)	
2 (9.21–14.8)	5.07 (4.88, 5.24)	0.08	5.86 (5.76, 5.95)	0.56	309.39 (305.08, 313.71)	0.08
3 (≥ 14.8)	4.82 (4.63, 5.02)	0.006	5.90 (5.79, 6.00)	0.11	303.45 (298.78, 308.13)	0.82
p-trend **	**0.005**		0.13		0.85	
HCB (n = 338)						
1 (≤ 41.9)	4.92 (4.72, 5.12)		5.94 (5.84, 6.05)		309.82 (304.92, 314.73)	
2 (41.91–59.9)	5.17 (5.00, 5.34)	0.09	5.85 (5.76, 5.94)	0.34	303.78 (299.61, 307.94)	0.85
3 (> 59.9)	4.95 (4.76, 5.14)	0.88	5.77 (5.67, 5.88)	0.04	303.82 (298.14, 307.51)	0.06
p-trend **	0.99		**0.03**		0.07	
β-HCH (n = 339)						
1 (< 39.9)	4.98 (4.76, 5.19)		5.93 (5.81, 6.04)		309.60 (304.38, 314.82)	
2 (39.91–56.6)	5.06 (4.89, 5.23)	0.72	5.82 (5.72, 5.91)	0.69	303.94 (299.76, 308.12)	0.91
3 (≥ 56.6)	5.02 (4.84, 5.21)	0.77	5.83 (5.73, 5.93)	0.24	303.12 (298.58, 307.66)	0.08
p-trend **	0.87		0.36		0.13	

* Adjusted for home score at 18 months, parity, maternal age and maternal education. Pesticides lipid-adjusted with units ng/g lipid.

** P-trend based on a scored variable using the median value of each tertile.

*** P-values based on the comparison between the category with the lowest category (referent).

Table 5

Association between maternal organochlorine pesticide exposure and communication development scores in daughters at 38 months by strata of maternal depression score.*

Analyte Tertiles (ng/g lipid)	Communicative Adjusted mean (95% CI)	p***	Intelligibility Adjusted mean (95% CI)	p***	Language Adjusted mean (95% CI)	p***
EPDS ≤ 6						
p,p'-DDT (n = 179)						
1 (≤ 9.2)	5.25 (4.98, 5.52)		5.78 (5.67, 5.88)		304.40 (297.32, 311.49)	
2 (9.21–14.8)	5.01 (4.79, 5.24)	0.06	5.97 (5.88, 6.06)	0.83	308.81 (302.82, 314.80)	0.56
3 (≥ 14.8)	4.71 (4.48, 4.93)	0.004	5.96 (5.87, 6.04)	0.01	306.26 (300.29, 312.23)	0.71
p-trend**	**0.002**		0.06		0.94	
EPDS > 6						
p,p'-DDT(n = 146)						
1 (≤ 9.2)	5.22 (4.93, 5.52)		5.77 (5.58, 5.95)		301.77 (295.26, 308.28)	
2 (9.21–14.8)	5.16 (4.86, 5.46)	0.46	5.70 (5.52, 5.89)	0.25	309.32 (302.73, 315.92)	0.08
3 (≥ 14.8)	5.00 (4.64, 5.36)	0.33	5.85 (5.63, 6.07)	0.49	298.72 (290.88, 306.55)	0.68
p-trend**	0.31		0.46		0.65	

Significant interactions ($p < 0.05$) for EPDS depression score and p,p'-DDT for communicative (pint = 0.007), intelligibility (p-int < 0.0001), and language (pint = 0.003).